In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

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DILLON COPENHAVER and AMANDA COPENHAVER, on behalf of their deceased minor child, NICHOLAS COPENHAVER,	*	No. 13-1002V Special Master Christian J. Moran
Petitioners,	*	Filed: May 31, 2016
v.	*	Entitlement; sudden infant death syndrome (SIDS); expert qualifications
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	
* *		

Andrew Downing, Van Cott & Talamante, PLLC, Phoenix, AZ, for petitioners; Claudia B. Gangi, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

This case presents a tragic story. When Nicholas Copenhaver was four months and, by all accounts, healthy, he was seen by his pediatrician. The pediatrician administered a set of vaccinations. In the early morning hours three days later, Nicholas died. After an autopsy discovered no other reason for Nicholas's death, the medical examiner classified it as a case of sudden infant death syndrome ("SIDS").

[1] The E-Government Act, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services), requires that the Court post this decision on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

Nicholas's parents, Dillon and Amanda Copenhaver, are the petitioners. They claim that the vaccinations that he received within 72 hours of his death caused his demise. The Copenhavers seek compensation through the National Childhood Vaccine Injury Compensation Program, codified at 42 U.S.C. § 300aa−10 through 34 (2012).

To support their claim, the Copenhavers rely upon the opinions presented by Doctors Douglas Miller, a neuropathologist, and David Axelrod, an immunologist. Dr. Miller and Dr. Axelrod opine that the vaccinations prompted the production of cytokines and that these vaccine-induced cytokines prevented Nicholas from rousing himself during an episode of respiratory distress.

In opposition, the Secretary also presented testimony from two experts: Doctors Brent Harris, a neuropathologist, and Christine McCusker, a pediatric immunologist. Dr. Harris and Dr. McCusker stated that it is less likely than not that the vaccinations stimulated the production of cytokines that interfered with Nicholas's brain function, causing him to die.

These four doctors testified at a hearing held on July 30-31, 2015. Other witnesses were Ms. Copenhaver and the person caring for Nicholas the night he died, Janice Schoneboom. Following the hearing, each party submitted one brief.

The case is ready for adjudication. For the reasons discussed at length below, the Copenhavers have not presented a persuasive case. The simplest explanation is that Dr. McCusker, one of the Secretary's experts, possesses greater training and experience to discuss the critical issues. Therefore, Dr. McCusker's opinion — that vaccines, given in the periphery, are unlikely to stimulate the production of cytokines that interfere with the brain's function — is given a greater amount of weight than the contrary opinions.

Everything below expands upon the above summary. To facilitate this expansion, the discussion is divided into four sections: background, standards for adjudication, analysis, and conclusion.

Background

To appreciate the analysis below, it is necessary to have background on SIDS, the facts of the case, and the petitioners' theory of how vaccination caused Nicholas's death.

1. Sudden Infant Death Syndrome (SIDS)

The age of four months is when the American Academy of Pediatrics recommends that babies receive a set of vaccinations. The age of four months is also a peak time period in which currently healthy babies are found dead after being asleep. When that death remains unexplained after a thorough clinical analysis, autopsy, and investigation of the death scene, doctors classify the death as one of sudden infant death syndrome. Exhibit 29 (Hannah C. Kinney et al., Medullary Serotonergic Network Deficiency in the Sudden Infant Death Syndrome: Review of a 15-Year Study of a Single Dataset, 60(3) J. Neuropathology and Experimental Neurology 228 (2001)) at 228; see also Dorland's Illus. Med. Dictionary at 1850 (32nd ed. 2012); Cozart v. Sec'y of Health & Human Servs., No. 00-590V, 2015 WL 6746616, at *4 (Fed. Cl. Spec. Mstr. Oct. 15, 2015), mot. for recons. denied, 2015 WL 6746499 (Fed. Cl. Spec. Mstr. Oct. 15, 2015), mot. for rev. denied, 2016 WL 1165978 (Mar. 9, 2016).

In the United States in 2001, the incidence of SIDS was 0.8 per 1000 live births. Exhibit 29 (Kinney) at 228; see also Cozart, 2015 WL 6746616, at *4; Tr. 138. In Germany, the incidence was 0.663 per 1000 live births. Exhibit 44 (Rüdiger von Kries et al., Sudden and Unexpected Deaths After the Administration of Hexavalent Vaccines (Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B, *Haemophilus Influenzae* Type B): Is There a Signal?, 164 Eur. J. Pediatrics 61 (2005)) at 62. For other information about the incidence of SIDS, see Cozart, 2015 WL 6746616, at *4.

Given these devastating deaths, researchers have been attempting to determine why SIDS happens. In 1994, James J. Filiano and Hannah C. Kinney co-authored an article that proposed that three separate factors coincide in cases of SIDS. Exhibit 28 (James J. Filiano and Hannah C. Kinney, A Perspective on Neuropathology Findings in Victims of the Sudden Infant Death Syndrome: The Triple-Risk Model, 65 Biology of the Neonate 194 (1994)). Dr. Filiano's and Dr. Kinney's triple risk model has become widely influential. The three factors are:

(1) a vulnerable time period, such as when a baby develops homeostatic control, (2) a vulnerable infant, such as one with an intrinsic defect in the brain, and (3) an external stressor. Id. at 195.

The vulnerable period for development of homeostatic control usually begins at approximately two months and continues until approximately six months. In this time, "major changes occur in virtually all physiologic systems as infants attain adaptive mechanisms enabling them to maintain homeostasis. These changes include dramatic transitions in homeostatic systems regulated by the brain notably autonomic control, ventilation, sleep-waking state organization, temperature regulation, and circadian rhythms." Id. at 195-96.

For the intrinsic defect, Dr. Kinney and other researchers have focused on a part of the brain that controls respiration known as the medulla oblongata. Tr. 125; Dorland's at 1121. The medulla oblongata sits on top of the spinal cord. Dorland's at 246. The specific portion of the medulla oblongata that is responsible for sensing the amount of carbon dioxide in the blood is known as the arcuate nucleus. Tr. 125; see also Dorland's at 1295. The arcuate nucleus transmits signals using serotonin, also known as 5-hydroxotryptamine (5-HT). Tr. 126. Autopsies of infants who have died of SIDS have revealed that approximately 70 percent have some defect in the 5-HT system. Tr. 126; but see Tr. 456-57 (Dr. Miller noting that in 1992, autopsies found a defect in only five percent of children who died of SIDS).

The third factor in the triple-risk model is an extrinsic stressor. Tr. 126-28 (Dr. Miller), 356-57 (Dr. McCusker). In Dr. Filiano's and Dr. Kinney's 1994 article, they proposed that prone sleeping could contribute to SIDS deaths. Relying upon epidemiological studies, they also identified minor respiratory or gastrointestinal illnesses, fever, and over-blanketing as other external stressors. Exhibit 28 at 196. The ensuing "Back-to-Sleep" campaign, which encouraged parents to place their babies to sleep in the supine, or face up, position, reduced the incidence of SIDS by approximately 50 percent. Tr. 127-28; see also Tr. 383. In a 2009 article, Dr. Kinney recognized that supine sleeping eliminated some of the potentially hazardous effects of prone sleeping, such as airway compression or rebreathing of exhaled gases. Nevertheless, babies still died from SIDS. Factors that placed an infant at risk include "bed clothes that covered the head, sleeping on sofas or other soft furniture in which the infant could become wedged, a high

ambient temperature in sleeping environment, soft bedding, and bed sharing." Exhibit J (Hannah C. Kinney and Bradley T. Thach, The Sudden Infant Death Syndrome, 361(8) New Eng. J. Med. 795 (2009)) at 3.[2] Mild infections continue to be listed as well. Id. at 4.

Dr. Kinney's articles have not included vaccinations among external stressors that could precipitate a SIDS death. Tr. 160-61 (Dr. Miller), 427-28 (Dr. McCusker). The Secretary's expert, Dr. McCusker, interprets Dr. Kinney's work as focusing on impediments in the mechanical aspects of breathing. Tr. 380-81. According to Dr. Miller, Dr. Kinney has told him that she is consciously staying away from the issue of whether vaccines cause SIDS. Tr. 189.

However, other researchers have explored a possible connection between vaccination and SIDS using large databases.[3] The Secretary advanced a study that found that the risk of SIDS was not increased in the 14 days after a hexavalent vaccination. Exhibit Y (M.M.T. Vennemann et al., Sudden Infant Death Syndrome: No Increased Risk After Immunisation, 25 Vaccine 336 (2007)) at 336.[4] Over a three-year period, German investigators identified 404 SIDS cases, and of which 333 families were interviewed, and of which immunization information was available for 307 cases. The researchers compared the health history of these 307 SIDS cases to the health history of 971 controls. Id. at 338; see also Tr. 364-68 (Dr. McCusker). The Vennemann group concluded that their study "further support[ed] that immunisations may reduce the risk of SIDS." Exhibit Y at 340. Although Dr. Miller offered some criticisms (see Tr. 137-41, 272-74), his most effective point was that the Vennemann group did not include a power analysis.

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[2] Because the Secretary submitted an author's manuscript, this decision cites to those page numbers, not the page numbers to the article as published.

[3] Special masters in the Vaccine Program have periodically considered whether vaccines caused SIDS. For a partial list of cases, see Cozart, 2015 WL 6746499, at *9.

[4] Hexavalent vaccines contain antigens to protect against polio, diphtheria, tetanus, pertussis, *Haemophilius influenzae type b*, and hepatitis B. Exhibit Y at 337.

The Vennemann group's suggestion that vaccinations may decrease the incidence of SIDS is consistent with a finding the Institute of Medicine made in 1991. The IOM stated that "All controlled studies that have compared immunized versus nonimmunized children have found either no association or a decreased risk of SIDS among immunized children." Exhibit 48 (Institute of Medicine, Adverse Effects of Pertussis and Rubella Vaccines (Christopher P. Howson et al. eds. (1991))) at 140 (citations omitted).[5] However, the IOM's most recent report stated that "The evidence is inadequate to accept or reject a causal relationship between the diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and SIDS." Exhibit 50 (Institute of Medicine, Adverse Events of Vaccines Evidence and Causality (Kathleen Stratton et al. eds. (2012))) at 582.

Thus, no articles reliably demonstrate that vaccines increase the risk of SIDS.[6] Tr. 362. This gap does not necessarily preclude a finding in the Copenhavers' favor because a petitioner may present a persuasive case without epidemiology or articles. Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2005); Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 549 (Fed. Cir. 1994). The undersigned, therefore, will evaluate the medical records, scholarly articles, expert qualifications, and the witnesses' testimony. See 42 U.S.C. § 300aa−13 (requiring special masters to consider the record as a whole).

[5] Because Congress mandated the IOM report on the safety of vaccines, special masters may rationally rely upon it. Terran v. Sec'y of Health & Human Servs., 41 Fed. Cl. 330, 337 (1998), aff'd, 195 F.3d 1302, 1314 (Fed. Cir. 2000) (noting that the Secretary may rely upon reports from the Institute of Medicine in revising the Vaccine Table). However, in this case, Nicholas received different vaccines, and the Secretary did not elicit testimony about the 1991 IOM report.

[6] The petitioners filed some articles reporting an instance, or several instances, in which an episode of SIDS occurred within a few days of a vaccination. However, as Dr. Miller explained, case reports cannot establish causation. Tr. 166. Therefore, although these articles have been reviewed, they are not discussed.

2. Facts

With respect to Nicholas's medical history, the parties have relatively little, if anything, in dispute. The medical records and testimony showed the following:

On March 7, 2013, Nicholas was born. Exhibit 1 at 1. The associated pregnancy and birth were relatively routine. Tr. 17. Checkups at two weeks and two months were also routine. During the appointment at two months, Nicholas received a set of vaccinations. Exhibit 5 at 25-28. Ms. Copenhaver stated that after this set of vaccinations, Nicholas had a fever that Tylenol controlled. Tr. 19-20. Dr. Miller and Dr. Axelrod interpreted Nicholas's fever as a manifestation of a systemic response to the vaccination. Tr. 83 (Dr. Miller), 289-90 (Dr. Axelrod); see also Tr. 407 (Dr. McCusker).

On July 12, 2013, Nicholas went to his pediatrician for a four-month well baby appointment. Nicholas appeared to be healthy. He received a second round of vaccinations, including Pentacel, Prevnar 13, and Rotateq. Exhibit 5 at 24, 30.[7]

According to his mother, prior to his second set of vaccinations, Nicholas was a very active baby who liked to smile. Tr. 20. In contrast, after the July 12, 2013 vaccinations, Nicholas was unsettled, restless, fussy, and lethargic. Tr. 23; exhibit 1 at ¶ 5. Two to three hours after vaccination, Nicholas vomited extensively. Tr. 22-23, 34-35; but see exhibit 1 at ¶ 5 (Ms. Copenhaver's affidavit not describing any vomiting the day of vaccination). Throughout the weekend, Nicholas remained restless, lethargic, and ran a low-grade fever. Tr. 19, 25-26. These nonspecific symptoms could indicate that Nicholas was responding to the vaccination. Tr. 289-90 (Dr. Axelrod: systemic effects of cytokines can include fever and lethargy), 408-11 (Dr. McCusker).

In the evening of Sunday, July 14, 2013, the Copenhavers dropped Nicholas off with Ms. Schoneboom. Tr. 26-27. At approximately 1:00 AM, Nicholas

[7] Pentacel is the trademarked name for a vaccine against diphtheria, tetanus, pertussis, polio, and *Haemophilius influenzae* type b. Dorland's at 1406. Prevnar is the trademarked name for a vaccine against seven strains of pneumococcus. Id. at 1514. Rotateq is the trademarked name for a vaccine against the rotavirus. Id. at 1655.

awoke and was unhappy. To help him fall back to sleep, Ms. Schoneboom swaddled him in a blanket and held him up on her shoulder as she sat on a sofa watching television. Tr. 42-44.[8]

At approximately 4:00 AM, Ms. Schoneboom woke up and discovered that Nicholas was not breathing. Resuscitation was attempted and 911 was called. Sadly, efforts to revive Nicholas were unsuccessful. Exhibit 10 at 1-5; exhibit 11 at 1; Tr. 48.

On August 13, 2013, Karl Christopher Stacy conducted a general autopsy on Nicholas. Exhibit 2 at 1-6; Tr. 79.[9] Dr. Stacy referred the neuropathology to Dr. Miller, whom the Copenhavers later retained in this litigation. Dr. Miller's investigation revealed two problems in Nicholas's brain. The first was "a small malformation of one hippocampus, representing a potential cause for seizures." Exhibit 2 at 11. The second was swelling in the cerebellum. Id. at 10; Tr. 87-88, 113-17, 241.

Dr. Miller's neuropathologic examination was also significant for what was not found. Dr. Miller stated that a brain abnormality commonly found in SIDS cases, a defect in the arcuate nuclei, was not present. Exhibit 2 at 11; see also Tr. 179-81.

At the hearing, Dr. Miller testified that when he performed the neuropathology work on Nicholas he did not know that Nicholas had been

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[8] Before the hearing, the Secretary had argued that the way Nicholas was placed to sleep could have contributed to his death due to SIDS. See Resp't's Preh'g Memorandum, filed July 6, 2015, at 2, 8. During the hearing, Ms. Schoneboom imitated how she positioned Nicholas with a doll. Tr. 43-47. After the hearing, the Secretary did not make any argument about Nicholas's positioning before he died. See Resp't's Posth'g Br., filed Nov. 3, 2015. Under these circumstances, a detailed recitation about how Nicholas was positioned is not required.

[9] As part of the general autopsy, Dr. Stacy examined Nicholas's lungs and took tissue samples from them. Dr. Stacy did not see any abnormalities. However, after the Secretary's expert examined them, Dr. Harris found that the lungs showed signs of pneumonia. Much like the possibility of a problem with Nicholas's sleeping position, the Secretary appears to have abandoned any argument that pneumonia contributed to Nicholas's death.

vaccinated within three days of his death. Tr. 81-82. In the absence of information about Nicholas's recent vaccination, Dr. Miller's August 2013 neuropathology report proposed that Nicholas may have had a seizure. Exhibit 2 at 11. In this litigation, Dr. Miller has changed his position. He now states that the vaccinations contributed to Nicholas's death.[10] (Dr. Miller's current theory is addressed next.) Dr. Stacy's conclusion was that "the cause of death of this sudden unexpected death of Nicholas Copenhaver is most likely rebreathing due to sleeping situation." Exhibit 2 at 2; see also Tr. 182-83.

3. Overview of Petitioners' Theory

With support from their experts, Dr. Axelrod and Dr. Miller, the Copenhavers present a theory that builds upon the triple risk model. To restate, the triple risk model proposes that SIDS episodes can occur (1) during a vulnerable time, (2) in a vulnerable infant, such as one with an intrinsic neurological defect, and (3) after the introduction of an extrinsic stressor.

The Copenhavers most clearly express their theory on page 10 of their posthearing brief. There they state: "Vaccination acts as the exact same mechanism of injury as infection does in serving as an extrinsic risk factor through cytokine expression." Pet'rs' Posth'g Br., filed Oct. 1, 2015, at 10. Cytokines are biological molecules that signal other cells to do things. Cytokines were first identified as components of the innate immune system, and can be either pro-inflammatory or anti-inflammatory, depending on the type of cytokine. Tr. 88. They add more detail to their theory when they elaborate: "During infection, peripherally produced cytokines can cross the blood-brain barrier, bind to endogenous cycle receptors on neuronal populations that mediate stress responses in the hypothalamus and/or brainstem, and thereby determine sickness behavior, including blunted arousal and depressed respiration." Pet'rs' Posth'g Br. at 10.

The Secretary's recitation of the Copenhavers' theory is slightly different. Quoting Dr. Miller's initial report, the Secretary summarizes the theory as the

[10] Dr. Miller's change appears to have been caused by a change in information about Nicholas's vaccination history. Dr. Miller appears not to have changed his opinion for purposes of litigation.

vaccinations "'induced cytokine production, and those cytokines then acted in the brainstem which was already deficient in serotoninergic drive for respiratory effort, leading to an apneic episode from which he did not recover, i.e. SIDS.'" Resp't's Posth'g Br., filed Nov. 3, 2015, at 2, quoting exhibit 13 at 10.[11]

Although petitioners could have presented their theory more clearly, it appears that they are not maintaining that the vaccine-induced cytokines caused an "apneic episode."[12] To be sure, Dr. Miller's initial report cited two articles about apnea and cytokines: exhibit 36 (Lauritz Stoltenberg et al., Changes in Apnea and Autoresuscitation in Piglets After Intravenous and Intrathecal Interleukin-1β Injection, 22 J. Perinatal Med. 421 (1994)), exhibit 37 (J. Frederik Frøen et al., Adverse Effects of Nicotine and Interleukin-1β on Autoresuscitation After Apnea in Piglets: Implications for Sudden Infant Death Syndrome, 105(4) Pediatrics e52 (2000)). However, the petitioners did not elicit any testimony from Dr. Miller about either article during direct examination. There was only brief rebuttal testimony from Dr. Miller (Tr. 460-61) after Dr. McCusker testified about the articles in her direct testimony (Tr. 368-71). Furthermore, the petitioners did not cite either article or otherwise discuss apnea in their posthearing brief.

Because cytokine-induced apnea appears not to be part of the Copenhavers' theory, the undersigned is not entirely certain as to how their theory proceeds. After reviewing all the expert reports, the medical literature associated with the reports, the pretrial briefs, the testimony, and the posttrial briefs, the undersigned has determined that the Copenhavers are contending that (1) vaccinations induce the production of cytokines just as infections induce cytokines, (2) the cytokines travel through the blood stream and cross the blood-brain barrier to reach the part of the brain responsible for auto-resuscitation, (3) for some unknown reason, Nicholas stopped breathing, and (4) Nicholas's brain could not initiate the normal autoresuscitation process because cytokines, which were induced by the vaccination, impaired the brain's functioning. See Tr. 148 (Dr. Miller: "the

[11] The Secretary uses "see also" to reference Dr. Miller's testimony at pages 124-28. In this portion of his testimony, Dr. Miller is explaining the basic triple risk model.

[12] Apnea means "cessation of breathing." Dorland's at 116.

cytokine IL-1 beta has an inhibitory effect on the 5-HT network . . . and in a situation where there's apnea during sleep, then there will be a failure to recover from it"); Tr. 301 (Dr. Axelrod: "he had the vaccination, the cytokine levels increased, just as they do with infection; . . . they had a reason to cross the blood-brain barrier and to be elevated in the cerebrospinal fluid, just as they were in the Rognum study; and the rest is, . . . as described by Dr. Miller"); Tr. 471-72. With respect to step 3 — for some unknown reason, Nicholas stopped breathing— the undersigned emphasizes that the Copenhavers are not arguing that the vaccinations caused an apneic episode. With this clarification, the undersigned will assess the persuasiveness of this theory and its applicability to Nicholas's case in the sections below.

Standards for Adjudication

In the analysis section below, evidence in this case will be analyzed according to the following standards of adjudication.

A petitioner is required to establish her case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

Special Masters are fact finders that use their accumulated expertise to judge the individual merits of claims. See Hodges, 9 F.3d at 961; Munn v. Sec'y of

Health & Human Servs., 970 F.2d 863, 871(Fed. Cir. 1992). Thus, the probative value of the evidence, the credibility of the witnesses, and the relative persuasiveness of the competing medical theories of the case, are within their purview. Moberly, 592 F.3d at 1326 ("Finders of fact are entitled-indeed, expected- to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Lampe, 219 F.3d at 1361-62. Special Masters may use the Daubert framework for analyzing the admissibility of scientific, technical, or other specialized knowledge, and the rules of evidence require the testimony to have a reliable basis in the relevant discipline. Terran, 195 F.3d at 1316.

The elements of the Copenhavers' case are set forth in the often cited passage from the Federal Circuit's decision in Althen: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Analysis

The analysis below applies the above standards of adjudication. It focuses first on overall weaknesses in the petitioners' case, and then moves on to discuss petitioners' case within the Althen framework.

1. Weaknesses in Petitioners' Case

After considering all the evidence, the undersigned finds that the petitioners have failed to meet their burden of presenting a persuasive case that the vaccinations contributed to Nicholas's unfortunate death. Three reasons support this overall conclusion. First, the Secretary's expert, Dr. McCusker, was much better qualified to discuss cytokines. Second, the articles do not support the opinions Dr. Miller and Dr. Axelrod expressed. Third, there are gaps in the medical record for Nicholas that Dr. Miller fills with assumptions. Of these three reasons, the most significant are the first and second.

A. The Secretary's expert, Dr. McCusker, was much better qualified to discuss immunology than the Copenhavers' experts, Dr. Axelrod and Dr. Miller.

In considering the value of opinion testimony, special masters may consider the offeror's expertise. See Snyder v. Sec'y of Health & Human Servs., 553 F. App'x 994, 1000–02 (Fed. Cir. 2014) (special master's finding that respondent's experts were more persuasive due in part to their current practice in neurology compared to petitioner's expert who had no recent practice was not arbitrary or capricious); see also Tompkins v. Sec'y of Health & Human Servs., 117 Fed. Cl. 713, 719 (2014) (noting special master reasonably articulated one expert's relative lack of training and experience as a basis for not crediting the witness); Holmes v. Sec'y of Health & Human Servs., 115 Fed. Cl. 469, 490 (2014) (stating the special master was reasonable in considering a testifying expert's "research credentials in the field"); Locane v. Sec'y of Health & Human Servs., 99 Fed. Cl. 715, 727 (2011) (finding special master rationally credited an expert with specialization in the disease in determining when the petitioner's disease began), aff'd, 685 F.3d 1375, 1380 (Fed. Cir. 2012).

The greatest weakness in the Copenhavers' case was the disparity in the credentials among the expert witnesses (Dr. Axelrod, Dr. Miller, and Dr. McCusker) in immunology.[13] The focus on immunology is important because the parties dispute which field is most relevant.

The Copenhavers argue that testimony about the causes of SIDS should be reserved for neuropathologists who have performed autopsies in SIDS cases. Pet'rs' Posth'g Br. at 19. In their view, their theory "sound[s] in neuropathology, not immunology." Id. at 20. Because Dr. McCusker is not a pathologist, she lacks the qualifications to discuss articles written by specialists in this field. Id.[14]

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[13] As discussed below, the disputed topics are almost exclusively immunological. The parties largely agreed about the pathology and neuropathology. See Tr. 267. Thus, the qualifications of Dr. Harris, the Secretary's neuropathologist, are largely irrelevant.

[14] In connection with this argument, the Copenhavers propose a novel prequisite for experts intending to comment upon an article. The Copenhavers maintain that to testify about an

The Secretary answers that Dr. McCusker was qualified to address immunologic topics, such as whether the response to vaccination is the same as the response to infection. The Secretary adds that if anyone testified outside his or her area of specialty, it was Dr. Miller. Resp't's Posth'g Br. at 5-6.

The Secretary's argument is well-founded. The Copenhavers have proposed a theory in which vaccinations lead to the production of cytokines and the cytokines impair the brain's function. The Copenhavers essentially concede this point when they acknowledge that "part of [their] causation theory in this matter deals with cytokine expression following vaccination." Pet'rs' Posth'g Br. at 20. There is no doubt that questions about cytokines (What type? How many are produced? Are they present in the brain? Do cytokines cause damage or do cytokines respond to damage?) dominated the hearing. The Copenhavers' attempt to minimize the significance of immunology is not persuasive. See Cozart, 2015 WL 6746616, at *11 (stating that in a similar theory presented by Dr. Miller, "the role of cytokines is fundamental"). Having found that immunology is a relevant discipline, the undersigned will proceed to review the credentials of the witnesses who discussed immunologic topics.

(1) *Dr. Axelrod, Copenhavers' expert.*

In terms of the medical education that he received, Dr. Axelrod is roughly comparable to Dr. McCusker, discussed below. After graduating medical school, Dr. Axelrod was a resident for three and a half years. Tr. 281. He completed two fellowships, the first at McGill University in the Department of Clinical Immunology, and the second at the United States National Institutes of Health from 1980-82. Tr. 281; exhibit 16 (curriculum vitae) at 1.

At the beginning of Dr. Axelrod's medical career (1979), he received board certification in internal medicine and, three years later, received additional certification in rheumatology. In 1988, he became board certified in medical

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article, the expert must be trained in the same discipline as the authors of the article. Pet'rs' Posth'g B., at 19-20. However, they provide no justification for that requirement.

laboratory immunology. In 2011, he received his most recent board certification, which is in allergy and immunology. Exhibit 16 at 3; Tr. 282, 303.

For teaching, Dr. Axelrod was an associate professor in the division of rheumatology at the Medical College of Ohio from 1989-91. Exhibit 16 at 2; Tr. 283.[15] He was again an associate professor from 2007-10, when he worked at the New Jersey Medical School. In the last two years of that period, he was the interim director of the division of allergy, immunology, and rheumatology. Id. His final academic position was an associate professor at Oakland University from 2010-12. Exhibit 16 at 2; Tr. 283, 314-15.[16] He also held visiting professorships at other institutions.

For research, Dr. Axelrod's curriculum vitae lists 12 articles that appeared in peer-reviewed journals. From their titles, none seem to involve cytokines.

Since 2012, Dr. Axelrod has been working as a private practitioner in York, Pennsylvania. His patient population is "mostly older." Most have allergies, including some adverse reactions to drugs. Tr. 315. In the course of his employment, he reads journals that publish articles about cytokines. Tr. 316.

The Secretary did not object to Dr. Axelrod's expertise in the field of immunology. Tr. 286. However, the Secretary attempted to impeach his trustworthiness by eliciting testimony on cross-examination that he advertised his services as an expert witness in the Vaccine Program on the internet. Tr. 302-03. He also wrote letters to attorneys whose names appear on a list maintained by the Court of Federal Claims Clerk's Office. Most of his participation in the Vaccine

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[15] In his testimony, Dr. Axelrod described his academic appointments as being in the field of immunology. His curriculum vitae states that his role at Medical College of Ohio was within the department of rheumatology. The undersigned assumes that Dr. Axelrod's teaching of rheumatology encompassed immunologic components.

[16] Again, there is a slight discrepancy between Dr. Axelrod's curriculum vitae and his testimony. For Oakland University, Dr. Axelrod's C.V. states he was an "associate professor." In his testimony, he stated he was a visiting professor. The undersigned does not attribute any significance to the difference in titles.

Program derived from his letters, rather than the website. Tr. 317. Dr. Axelrod stated that he also communicated with the government but the government has not retained him. Tr. 302.

Dr. Axelrod's advertising of his services as an expert witness raises some concern. An advertisement could be construed as a willingness to provide an opinion that is helpful to the retaining party for the correct fee. However, after observing Dr. Axelrod's demeanor, the undersigned did not find that Dr. Axelrod was offering opinions simply to be paid. In other words, Dr. Axelrod appeared to be providing opinions that he held sincerely.

Although sincerity was not a problem with Dr. Axelrod, his lack of expertise in cytokines was. Dr. Axelrod was retained to opine about "cytokine production with vaccination." Tr. 287. Yet, on direct examination, his answers to questions were relatively short because the Copenhavers' attorney was asking leading (or narrow) questions. Consequently, Dr. Axelrod did not explain critical articles on immunology very well. The lack of persuasive testimony from Dr. Axelrod is most evident with respect to an article the Copenhavers were using to support their argument that the cytokine response to vaccination is similar to the cytokine response after infection. See Tr. 291-92, discussing exhibit 17 (Yasuyo Kashiwagi et al., "Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), *Haemophilus Influenzae* Type B (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines," 10(3) Human Vaccines & Immunotherapeutics 677 (2014)). The overall impression was that Dr. Axelrod could not testify knowledgeably about a topic — cytokines — that was both critical to the Copenhavers' theory and within his ostensible area of expertise. That impression, in turn, was further confirmed on cross-examination when the Secretary attempted to ask him a question about an article that studied cytokines and that Dr. Axelrod cited in his report. Dr. Axelrod stated that he "may have even overstepped my bounds." Tr. 310, discussing exhibit 23 (Hazim Kadhim et al., "Distinct Cytokine

Profile in SIDS Brain: A Common Denominator in a Multifactorial Syndrome?," 61 Neurology 1256 (2003)).[17]

The undersigned concurs that the field of cytokines was outside the bounds of Dr. Axelrod's expertise. As previously noted, his knowledge about cytokines appears to stem largely, if not entirely, from reading journal articles. He has not published any articles on cytokines or conducted research on them. This relative lack of expertise diminishes the value of Dr. Axelrod's opinions. See Snyder, 553 F. App'x 994, 1000–02 (noting the special master did not find persuasive the testimony of expert who read literature to support his opinion but did not actually treat patients with the relevant disease); Daubert v. Merrell Dow Pharm., Inc., 43 F.3d 1311, 1317 (9th Cir. 1995) ("[o]ne very significant fact to consider is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying").

Consequently, for all these reasons, the undersigned gives Dr. Axelrod's testimony about cytokines relatively little weight. This finding means that the Copenhavers' remaining expert witness, Dr. Miller, must be considered.

(2) *Dr. Miller, Copenhavers' expert.*

Preliminarily, it is important to emphasize that this portion of the decision is weighing the experts' qualifications to discuss immunology.[18] Dr. Miller works as a neuropathologist. Tr. 74-76.[19] The comments about Dr. Miller's knowledge and

[17] The petitioners did not cite exhibit 23, or any Kadhim article, in either their pretrial or posttrial brief.

[18] Again, for purposes of analysis, the undersigned assumes that Dr. Miller expressed opinions on the reasonable medical probability standard.

[19] In the normal course of his professional duties, Dr. Miller performed the neuropathological aspects of Nicholas's autopsy. Tr. 78-79; exhibit 2 at 11.

background about immunology should not be construed as any misgivings about Dr. Miller's abilities as a neuropathologist.

The basic definition of neuropathology is "the branch of medicine dealing with morphological and other aspects of disease of the nervous system." Dorland's at 1268. In turn, "morphology" concerns "the science of the forms and structure of organisms." Id. at 1181.

The Copenhavers have not presented an easily understood basis for finding that Dr. Miller's expertise in neuropathology gives him a basis for explaining immunology. Dr. Miller is familiar with SIDS as he has conducted the neuropathological aspects of an autopsy in approximately 100 cases. Tr. 188. This experience provides him a basis for identifying structural defects in the arcuate nucleus. However, to identify cytokines as affecting any structural defect is another step. Dr. Miller may have training and experience to take this step, but the Copenhavers have not made this aspect of his background readily apparent.[20]

On cross-examination, Dr. Miller stated that he is not board certified in immunology and he does not hold himself to be an expert in immunology. Tr. 154. Among his numerous publications, he has written one article involving cytokines. It was written in the late 1980's or early 1990's. Tr. 187.

Regardless of whether the topic was neuropathology or immunology, Dr. Miller testified without any objection from the Secretary. In other words, his lack of experience in immunology did not preclude the admissibility of his testimony. The question is about the weight to be given to his testimony.

To be clear, as shown in sections 1.B, 1.C, and 2, below, the undersigned is considering all the testimony and weighing the value of that testimony.

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[20] In response to a question from the undersigned, Dr. Miller stated that he "deal[s] with clinical and pathological correlation all the time." Tr. 188.

(3) ***Dr. McCusker, Secretary's expert.***

Dr. McCusker possesses an excellent background in immunology. Before attending medical school, she earned a master's degree in molecular virology and completed three years of study in a Ph.D. program for immunology. Tr. 330. After medical school, she did a residency in pediatrics and then a post-doctoral fellowship in allergy and immunology. Id.

She holds the Canadian equivalents of board certification in the field of pediatrics as well as the field of allergy and immunology. Tr. 331. As a clinician, she works at the McGill University Health Center, Montreal Children's Hospital, where she sees patients with problems in their immune system and with allergies. Tr. 333.

Dr. McCusker works at McGill University as an associate professor in the division of allergy and immunology within the department of pediatrics. Tr. 331; exhibit D (curriculum vitae) at 3. She teaches all the first year medical school students immunology and other topics. Tr. 333. She also teaches undergraduate students basic immunology and graduate students advanced immunology. Tr. 334. Her experience in teaching probably contributed to her ability to explain complicated topics and scholarly articles in a way that made them understandable.

Dr. McCusker conducts research in immunology. She operates her own laboratory, focused on developmental immunology. Tr. 331. Her curriculum vitae lists more than 30 articles published in peer-reviewed journals. Exhibit D at 21-25. Of these, approximately 15 publications involved cytokines. Tr. 335.

The Copenhavers did not object to Dr. McCusker's being recognized in the field of pediatrics and pediatric immunology, although the Copenhavers maintained that she could not testify in the field of neuropathology. Tr. 335. Although they did not challenge her credentials or experience, the Copenhavers attempted to portray Dr. McCusker as being biased in favor of companies that manufacture pharmaceuticals including vaccines. See Tr. 402-05; Pet'rs' Posth'g Br. at 18-19. However, the funding she has received from these companies appears to be a (natural) consequence of her expertise.

The undersigned did not perceive any bias from Dr. McCusker. She remained a superb witness. As the Secretary noted, many special masters have

praised Dr. McCusker's testimony. Resp't's Posth'g Br. at 5 n.3 (citing Brooks v. Sec'y of Health & Human Servs., No. 04-405V, 2015 WL 3799646, at *15 (Fed. Cl. Spec. Mstr. May 14, 2015); Cedillo v. Sec'y of Health & Human Servs., No. 98-916V, 2009 WL 331968, at *27-28 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), mot. for rev. denied, 89 Fed. Cl. 158 (2009), aff'd, 617 F.3d 1328 (Fed. Cir. 2010); Doe/11 v. Sec'y of Health & Human Servs., No. 99-212V, 2008 WL 4899356 (Fed. Cl. Spec. Mstr. Oct. 29, 2008), mot. for rev. denied, 87 Fed. Cl. 1 (2009), aff'd, 601 F.3d 1349 (Fed. Cir. 2010); Tosches v. Sec'y of Health & Human Servs., No. 06-192, 2008 WL 440285 (Fed. Cl. Spec. Mstr. Jan. 31, 2008)).

Dr. McCusker's testimony was largely, but not exclusively, about immunology generally, and cytokines specifically.[21] As discussed in section 1.B, below, immunology is where Dr. Axelrod and Dr. Miller fell well short of being persuasive. In sum, Dr. McCusker possesses a background in pediatric immunology that is superior to either Dr. Axelrod or Dr. Miller. She practices pediatric immunology every day. She has conducted research on cytokines, and written several papers on cytokines.

The strongest endorsement about Dr. McCusker's abilities came in the rebuttal phase of the case. During Dr. McCusker's testimony, the Copenhavers objected to portions of her testimony as being outside her area of expertise. The undersigned allowed her testimony and stated that "either Dr. Axelrod or Dr. Miller [can] explain why [Dr. McCusker's testimony] is wrong." Tr. 360. In rebuttal, the undersigned asked Dr. Axelrod whether any portion of Dr. McCusker's testimony was erroneous, and Dr. Axelrod replied: "I think I agree with most of what she had to say." Tr. 451. That endorsement is telling.

[21] A non-immunologic topic on which Dr. McCusker's testified was how infants breathe. Tr. 380-88, 416-18. Dr. McCusker's training in pediatrics qualifies her to testify about this topic. Tr. 431-32.

B. The medical literature on the effect of cytokines is not consistent with the Copenhavers' theory.

Along with the disparity in the experts' qualifications, the other major reason for finding the Copenhavers' claim unpersuasive is that the medical articles are more consistent with the Secretary's description of them.

According to binding precedent, petitioners may establish that they are entitled to compensation without presenting any medical literature. Althen, 418 F.3d at 1274. "However, it should be obvious to petitioner that a scientific theory that lacks any empirical support will have limited persuasive force." Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 134 (2011), aff'd without opinion, 463 F. App'x 932 (Fed. Cir. 2012). When literature is submitted, special masters may review the literature. Andreu, 569 F.3d at 1379. Special masters are not required to accept the opinion of any expert, particularly one who expresses opinions without support. Cedillo, 617 F.3d at 1347–48.

The Copenhavers' claim seems inconsistent with the submitted articles in two respects.

(1) *Extending the Triple Risk Model seems unwarranted.*

Dr. Kinney proposes that during a vulnerable time, children with a defect in their brain who encounter an external stressor may suffer a SIDS death. To date, the list of external stressors includes prone sleeping, co-sleeping, and infections. Exhibit 28 (Filiano and Kinney) at 196; exhibit J (Kinney and Thach) at 4, 7.

Through Dr. Miller and Dr. Axelrod, the Copenhavers extend the list of external stressors to include vaccinations. As mentioned earlier, none of Dr. Kinney's articles have included vaccinations. See Tr. 160-61, 357, 427-28.

As Dr. McCusker discussed extensively, almost all the external stressors in Dr. Kinney's work are factors that impair the mechanics of breathing. Tr. 380-81, 384-87. From her experience as a pediatrician working in an emergency room, Dr. McCusker knows how infants breathe. Tr. 431-32.

An impairment in breathing serves as the immediate trigger that leads to SIDS in the triple risk model. One example of a cause for problems in respiration

is an upper respiratory infection. The upper respiratory infection interferes with the infant's breathing and, during a critical age when the infant's brain is developing, the brain lacks the ability to arouse the infant. This sequence is easily understood.

The Copenhavers' theory alters the triple risk model. See Cozart, 2015 WL 6746616, at *8-9 (describing Dr. Miller's theory for how vaccines cause SIDS as "novel"). The Copenhavers attempt to equate infections with vaccinations. Pet'rs' Posth'g Br. at 10.

The Copenhavers are not persuasive because, at the most basic level, they have not presented any evidence that cytokines trigger problems in breathing. Infections, co-sleeping, and prone sleeping can all interfere with how the respiratory system functions. There is very little evidence, and certainly no persuasive evidence, that cytokines obstruct ventilation.

The Secretary distinguished the mechanical aspects of respiration from the neurochemical effects of vaccination. Resp't's Posth'g Br. at 3-4. It would have been helpful for the Copenhavers to have answered this argument in a reply brief. However, the Copenhavers did not file a reply, leaving the Secretary's argument unaddressed. Dr. Kinney's triple risk model sensibly includes as extrinsic risks factors that impair breathing. Dr. Axelrod's and Dr. Miller's attempt to expand the group of extrinsic risk factors to something (vaccination) that does not impair breathing is not sensible.

The Copenhavers' unpersuasive attempt to extend the extrinsic risk factor from Dr. Kinney's triple risk model stems from a difference in opinion about the factors that influence an infant's respiration. As a board-certified pediatrician, Dr. McCusker was much more qualified to explain how infants breathe and what can interfere with respiration than the Copenhavers' experts, who lacked similar expertise in pediatrics. The next topic also is based upon a field in which Dr. McCusker possesses excellent qualifications --- immunology.

(2) *The Copenhavers have not established that cytokines damage the brain's ability to respond.*

The second significant problem in the Copenhavers' case is that they propose that cytokines damage the brain, reducing its ability to respond to

stoppages in breathing. This assertion is based upon an incomplete and outdated understanding of cytokines, one that Dr. McCusker effectively refuted.

Before exploring the shortcomings in the Copenhavers' case regarding the damage that cytokines might cause, the undersigned will first discuss one idea that the Copenhavers did establish persuasively. The Copenhavers showed that the immune system can produce roughly the same quantity of a cytokine known as IL-6 in response to the influenza vaccination as it produces in response to an influenza infection.

The body's encounter with an outside substance, known as an antigen, leads to a response from the immune system. Dorland's at 103. At this "big picture" level, infections and vaccinations are similar: they both prompt the immune system to respond. Tr. 131, 162 (both Dr. Miller), 317-18 (Dr. Axelrod). The immune system's response includes the production of cytokines. Tr. 377-78, 426 (both Dr. McCusker).

For the general proposition that vaccines and infections prompt a comparable amount of cytokines to be produced, Dr. Miller and Dr. Axelrod rely upon the Kashiwagi article. Tr. 135-36, 172, 204, 291, 304. The Kashiwagi researchers, in part, determined "whether cytokines were produced in the serum after immunization," including IL-1β, IL-6, and TNF-α. Exhibit 17 at 680. In the portion of the experiment on which Dr. Miller and Dr. Axelrod rely, the Kashiwagi researchers presented the cytokine measurements, in picograms / milliliter (pg/mL), of four groups of people: (1) those immunized without a febrile reaction, (2) those immunized with a febrile reaction, (3) those infected with 2009 H1N1 pandemic influenza who were outpatients, and (4) those infected with 2009 H1N1 pandemic influenza who were admitted patients.[22] See exhibit 17 at 680, 682 (table 3).

[22] Petitioners relied on other studies to show the effects of cytokines, but at the much larger nanogram, as opposed to picogram, level (for reference, one picogram = .001 nanogram). See exhibit 52 (Keither D. Rochfort et al., Downregulation of Blood-Brain Barrier Phenotype by Proinflammatory Cytokines Involves NADPH Oxidase-Dependent ROS Generation:

In consolidated chart form, the data appear as follows:

	Cytokine Profiles in pg/mL (95% Confidence Interval)	
	IL-1ß	IL-6
Immunized w/o febrile reaction	1.12 (0.04~2.21)	13.43 (-5.05~31.91)
Immunized w/ febrile reaction	.68 (.36~.99)	29.44 (17.35~41.53)
H1N1 Infected Outpatient	.8 (0-2.06)	19.5 (1.54-37.45)
H1N1 Infected Admitted	19.44 (0-54.29)	35.93 (19.19-52.66)

The Kashiwagi researchers stated "no significant difference was observed in the IL-6 and TNF-α levels between the influenza outpatients and immunization groups with febrile or non-febrile illness after vaccination." Id. at 680. Thus, Kashiwagi supports the proposition that the amount of IL-6 that is produced after vaccination is comparable to the amount of IL-6 that is produced after an infection with H1N1. Pet'rs' Posth'g Br. at 13.

That specific proposition, however, cannot be generalized to establish that the vaccines in this case resulted in production of a comparable amount of a different cytokine (IL-1β) as would have resulted from an infection. See exhibit 17 at 680, 682 (table 3, which is reproduced above). In fact, the Kashiwagi researchers did not conclude that vaccination can result in a comparable amount of IL-1β cytokine. Dr. McCusker highlighted this discrepancy, explaining : "the problem is that in – for purposes of the conversations, we've been using the [word] 'cytokines' as if they're all the same, and the truth is they're not."

At this more sophisticated level of analysis, information about how individual cytokines act becomes critical, and Dr. McCusker's superior background in immunology showed through. See Cozart, 2015 WL 6746499 at *7. Simply, she raised characteristics about cytokines that are not compatible with the

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Consequences for Interendothelial Adherens and Tight Junctions, 9:7 Plos One (2014)) at 6; Tr. 309.

Copenhavers' theory, and further opined that cytokines in an infant's brain are unlikely to cause damage.[23]

In the triple risk model, a SIDS victim can have an inherent defect in some part of his brain, and oftentimes this defect is in the arcuate nucleus. See exhibit 28 (Filiano and Kinney) at 196, exhibit J (Kinney and Thach) at 6, 15. The Copenhavers generally propose that vaccine-induced cytokines worsen the brain's function – either by changing a previously functioning brain into a non-functioning one or by making a poorly functioning brain perform worse. See Pet'rs' Posth'g Br. at 10.

Years ago, some research provided support for this idea. Dr. Kinney and other researchers discovered the presence of certain cytokines in the brains of infants who died from SIDS. See exhibit 38 (Hazim Kadhim et al., Distinct Cytokine Profile in SIDS Brain, 61 Neurology 1256 (2003)); exhibit 20 (Ingvar Jon Rognum et al., Interleukin-6 and the Serotonergic System of the Medulla Oblongata in the Sudden Infant Death Syndrome, 118(4) Acta Neuropathologica 519, 519 (2009)); Tr. 132, 177, 194, 296-97, 353-57 (all discussing Rognum), 358, 452-53 (discussing Kadhim). This discovery led to the hypothesis that the cytokines were causing the death. Tr. 345.

However, more recent research contradicts that hypothesis. Some cytokines occur in the brain normally. See Tr. 89 (Dr. Miller), 202-04 (Dr. Miller), 267 (Dr. Harris). Thus, the simple presence of cytokines does not mean that the cytokines cause injury.

The cytokines may be present in the brain because they are responding to an injury, that is, the cytokines are beneficial, not harmful. Dr. Kinney and colleagues asserted in 2009 that elevated levels of IL-6 "may reflect a compensatory mechanism whereby defective arcuate 5-HT neurons require excessive cytokine stimulation to respond to infection-induced hypercapnia." Exhibit 32 (Hannah C.

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[23] Dr. McCusker acknowledged that cytokines produced in the body's periphery can affect the brain's function. She provided the example of a fever after vaccination. See Tr. 348-50 (discussing active transport), 422-24, 445-48.

Kinney et al., The Serotonergic Anatomy of the Developing Human Medulla Oblongata: Implications for Pediatric Disorders of Homeostasis, 41 J. of Chemical Neuroanatomy 182 (2011)) at 195; Tr. 354, 440.

Dr. McCusker concisely explained how Dr. Kinney was using IL-6. She stated that IL-6 was a message, like words being spoken into a telephone. The telephone in this analogy is the part of the brain that normally receives the cytokine signals, for example the arcuate nucleus. With SIDS, the arcuate nucleus does not work. To continue Dr. McCusker's analogy, the telephone is unplugged and therefore cannot receive the message the IL-6 is trying to transmit. Tr. 442; see also Tr. 195-96 (Dr. Miller describing signals and receptors without analogy to a telephone). Thus, the problem is with the receiver (the arcuate nucleus), not the signal, and the signal (the increased amount of IL-6) is an effect of the problem with the receiver, not the cause.

At the hearing, the undersigned was impressed with Dr. McCusker's interpretation of the 2009 Kinney article. Thus, the undersigned specifically inquired about the Kinney article in Dr. Axelrod and Dr. Miller's rebuttal testimony. When asked about whether IL-6 was compensatory, Dr. Axelrod stated that he did not have the expertise to answer any questions. Tr. 454. Dr. Miller stated: "I don't disagree that it's [IL-6 is] not causative." Tr. 471. Thus, the rebuttal testimony essentially leaves Dr. McCusker's opinion that IL-6 responds to damage, rather than causes the damage, unrebutted.[24]

C. The Copenhavers' case assumes facts about Nicholas.

The foregoing reasons explain why the Copenhavers have failed to present a persuasive case that vaccinations can cause SIDS. Even if they had succeeded,

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[24] When Dr. Miller "didn't disagree" that IL-6 was not causative, he stated that the cytokine that is more likely to be responsible for causing damage is IL-1β. Tr. 471. However, a foundation for the Copenhavers' theory is that the expression of cytokines after infections corresponds to the expression of cytokines after vaccination. The Kashiwagi article supports this assertion for IL-6, but the accuracy of this assertion with respect to IL-1β is much less clear. Dr. Miller cannot mix-and-match from one cytokine to another.

they would still be required to establish that Nicholas responded to the vaccinations in a way their theory predicted.

With respect to Nicholas, the Copenhavers' case contains two assumptions that make crediting their case difficult. The first assumption concerns his brain, and the second assumption concerns his cytokine levels.

(1) ***Whether Nicholas's brain was defective.***

One of the factors in Dr. Kinney's triple risk hypothesis is that infants are vulnerable to SIDS when they have an intrinsic defect in their brains. Dr. Kinney's group has focused attention on the arcuate nucleus, which is located in the medulla portion of the brain stem.

As part of the autopsy for Nicholas, Dr. Miller analyzed Nicholas's brain. He obtained tissue samples that he looked at under a microscope. Tr. 189-93. Dr. Miller's neuropathological report states: "Examination of the medulla reveals a robust arcuate nucleus." Exhibit 2 at 11; accord Tr. 166-67. The neuropathological report continues: "Thus, while the most common brain abnormality associated with Sudden Infant Death Syndrome is not present here (absence or hypoplasia of the arcuate nuclei), the hippocampal abnormality represents a potential cause of sudden death through a seizure." Exhibit 2 at 11.[25] In this litigation, the Secretary's expert in neuropathology, Dr. Harris, had an opportunity to view the tissue samples that Dr. Miller had prepared. Dr. Harris also did not find any defect in Nicholas's arcuate nucleus. Tr. 241, 269.

In this litigation, Dr. Miller assumes that Nicholas had some defect in his brain. This assumption is based upon two factors. First, Dr. Kinney has identified defects in the arcuate nucleus in approximately 70 percent of SIDS cases when she used advanced receptor autoradiography techniques. Dr. Miller did not use any advanced technique in Nicholas's case. Thus, this leaves open the possibility that more sophisticated screening would have found a defect that Dr. Miller's routine

[25] Dr. Miller testified that the abnormality he found in the hippocampal region does not affect his opinion. Tr. 169.

work did not. Tr. 168-69. Second, during the neuropathologic portion of the autopsy, Dr. Miller identified a problem in Nicholas' cerebellum. Exhibit 2 at 10. From this finding, Dr. Miller reasoned that Nicholas probably suffered some injury in utero and this injury could have produced other lesions that have not been identified. Tr. 167.

Dr. Harris was not willing to assume that Nicholas suffered from an unfound defect in his brain. In his view, Nicholas's case should not be classified as SIDS (meaning sudden infant death syndrome), but rather sudden unexpected death syndrome. Tr. 241, 269. Dr. Harris could not offer any explanation for why Nicholas died. Tr. 263.

Overall, Dr. Miller's determination that Nicholas's medulla was robust (exhibit 2 at 11) is a matter of some concern. The lack of an abnormality appears to have led Dr. Miller to think that Nicholas did not die from SIDS. Exhibit 2 at 11. Dr. Miller's colleague, Dr. Stacy, described Nicholas as suffering from "sudden unexpected death[,]" which is similar to the wording Dr. Harris proposed. Id. at 2. The Copenhavers' case would be stronger if a neuropathologist located a defect in Nicholas's medulla as the triple risk model proposes.

(2) *Whether cytokines were present in Nicholas's brain.*

A second aspect of the Copenhavers' theory is that cytokines degraded the function of Nicholas's brain. Pet'rs' Posth'g Br. at 10. When asked whether Nicholas produced any cytokines, Dr. Miller stated that he did not know because routine autopsies do not include an investigation for cytokines. Tr. 90.

Dr. Miller predicted that if a test were done, it is "plausible" that IL-6 would be found in Nicholas's brain. Tr. 178-79. Dr. Miller and Dr. Harris agreed that a type of immunohistochemical testing described in the Rognum article could still be performed on the tissues from Nicholas's testing. Tr. 193-94, 268-69.

Overall, the lack of evidence showing that Nicholas actually responded in a way that Dr. Miller and Dr. Axelrod predicted is an obstacle to awarding the Copenhavers compensation. See Moberly, 592 F.3d at 1324 (the petitioners' expert "conceded that there was no evidence in the record suggesting that the proposed mechanism was at work in [the child's] case. Accordingly, the special

master did not err in concluding that the blood-brain barrier theory did not support the petitioners' claim of causation."); Cozart v. Sec'y of Health & Human Servs., 2016 WL 1165978, at *6 ("As Dr. Oleske's theory directly relies on the presence of pro-inflammatory [cytokine] response, and none was noted in [the child], it would follow that Dr. Oleske's theory that [the child] died as a result of his October 19, 1998, vaccines is unsupported."). However, the two previously identified deficiencies collectively create the large majority of the petitioners' significant shortfall in meeting their burden. Under this circumstance, the unsupported assumptions about Nicholas are superfluous to the outcome.

To restate, the undersigned finds that the Copenhavers failed to carry their burden of presenting a persuasive case for three reasons. First, Dr. McCusker's superior experience in immunology make her opinions about immunology more reliable than the opinions from either Dr. Axelrod or Dr. Miller on immunology. Second, the literature does not support the opinions Dr. Axelrod and Dr. Miller presented. Third, the Copenhavers filled gaps in knowledge about Nicholas with assumptions. These reasons underlie an analysis of the Althen factors.

2. Althen Analysis

The required elements for the Copenhavers' case set forth in Althen are: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

A. Prong one, medical theory.

The first prong from Althen requires the petitioners to establish "a medical theory causally connecting the vaccination and the injury." Althen, 418 F.3d at 1278. The Court of Federal Claims has interpreted this portion of Althen as requiring not simply the presentation of a theory, but the presentation of a persuasive theory. M.S.B. by Bast v. Sec'y of Health & Human Servs., 117 Fed. Cl. 104, 123 (2014), appeal dismissed, 579 F. App'x 1001 (Fed. Cir. 2014); Taylor v. Sec'y of Health & Human Servs., 108 Fed. Cl. 807, 819 (2013).

Largely for the reasons explained in section 1A and 1B, above, the Copenhavers have failed to present a persuasive theory. To Dr. Kinney's triple risk model, the Copenhavers have added vaccination to the list of extrinsic risk factors. However, vaccinations are unlike the other extrinsic risk factors because the ones Dr. Kinney proposes interfere with breathing. The Copenhavers have failed to persuade the undersigned that vaccinations are the equivalent of upper respiratory infections.

In finding that the Copenhavers have failed to meet their burden of proof, the undersigned has considered the testimony of Dr. Harris that the Copenhavers cited twice in their brief. The Copenhavers argue that Dr. Harris admitted the reliability of their theory. Pet'rs' Posth'g Br. at 11, 15-16. The relevant portion of Dr. Harris's testimony on cross-examination is:

> [M]y question is more if it's possible that vaccination could serve as an inciting event, one prong of the three-prong triple-risk theory, if it's possible, and you have a child that gets multiple vaccinations 2 1/2 days before death with manifested symptomatology -- which we've already described as a change in his physiology -- is it reasonable to assume that vaccination may have played a role in inciting his death?
>
> A. If there are no other intrinsic -- excuse me, no other extrinsic factors that could be called into play, I would consider it.

Tr. 262 (emphasis added).

This portion of Dr. Harris's testimony and the persuasiveness of the Copenhavers' argument about it turn on the meaning of "consider." In a dictionary, "consider" has different meanings. Definitions include:

1. To think about carefully and seriously,

2. To regard as, think or deem to be: *considered her a fool.*

3. To believe after deliberation; judge: *considers waste criminal.*

The American Heritage Dictionary 313 (2d Coll. Ed. 1985). The Copenhavers' argument seems based upon Dr. Harris using "consider" in its third sense.

However, Dr. Harris's demeanor while testifying suggested that he was using "consider" in its first sense, meaning that he would contemplate whether vaccines could serve as an extrinsic risk factor. The idea that Dr. Harris would reflect carefully and seriously is consistent with the Copenhavers' attorney's use of the word "possible" in the preamble to the question. Moreover, in another place in his testimony, Dr. Harris unambiguously discounted the vaccinations as contributing to Nicholas's death. Tr. 225.

In any event, even if Dr. Harris's statement served as an admission on his part, the Copenhavers would still be required to grapple with Dr. McCusker's opinion. Dr. McCusker persuasively refuted the assertion that IL-6 cytokines are likely to damage the medulla. Dr. McCusker explained that IL-6 cytokines are more likely part of the restorative process. This finding removes another aspect of the Copenhavers' theory, making their theory unpersuasive.

B. Prong two, logical sequence.

The second prong of Althen requires "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278.

Here, as a matter of logic, because the Copenhavers have not presented a persuasive basis for finding that vaccinations can cause SIDS, they have also not presented any persuasive basis for finding that the vaccinations caused Nicholas to die from SIDS. See Caves, 100 Fed. Cl. at 134.

In connection with prong 2, the Federal Circuit has instructed special masters to consider carefully the views of treating doctors. Capizzano, 440 F.3d at 1326. Here, neither Dr. Stacy nor Dr. Miller mentioned that Nicholas was vaccinated in their reports from the autopsy and neuropathological autopsy. See Exhibit 2 at 2, 11. Dr. Miller's omission is understandable because when he conducted the neuropathological autopsy, he did not know that Nicholas was recently vaccinated. Tr. 81-82. Thus, it seems likely that Dr. Stacy also did not know about the recent vaccinations.

When the treating doctors do not know about the vaccination, any lack of connection between the vaccination and injury should not be held against the petitioners. Dr. Stacy's autopsy is not given probative weight, although it has been considered.

After Dr. Miller joined the litigation and learned about the vaccination, he rendered an opinion favorable to the Copenhavers' position. His opinion is not persuasive for the reasons set forth above. See Doyle v. Sec'y of Health & Human Servs., 92 Fed. Cl. 1 (2010). For these reasons, the Copenhavers have not met their burden regarding prong 2.

C. Prong three, timing.

The third prong of Althen requires "a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278. As part of her case-in-chief, the petitioner bears the burden of establishing that the onset of her disease occurred within an acceptable time. Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). This formulation implies that the third prong from Althen actually contains two parts. First, there must be a showing that a range of time is "acceptable" to infer causation. Second, there must be a showing that the vaccinee's disease arose in this acceptable time. Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542–43 (2011), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff'd per curiam, 503 F. App'x 952 (Fed. Cir. 2013).

Here, the parties devoted relatively little attention to this prong. Before the hearing, Dr. Miller appeared to suggest that vaccinations could cause an increase in cytokines for approximately 48 hours after vaccination. Exhibit 13 (Dr. Miller's report) at 8; see also Pet'rs' Preh'g Br., filed June 12, 2015, at 16. At hearing, without much elaboration, Dr. Miller stated: "I would find it implausible to push much beyond four days and with . . . a peak risk, around two days." Tr. 142. Because Nicholas died approximately two and a half days after vaccination, his death occurred within the temporal window Dr. Miller predicted.

The Secretary did not contest Dr. Miller's proposed timeframe. Consequently, the Copenhavers have carried their burden regarding prong 3, meaning that they established Nicholas died within the time predicted by the theory.

As explained above, however, the Copenhavers have not presented a persuasive theory explaining how vaccines can cause an infant to die unexpectedly. In the absence of a persuasive theory, the finding that the temporal sequence of events is appropriate does not advance the Copenhavers' case in any meaningful sense. See Langland v. Sec'y of Health & Human Servs., 109 Fed. Cl. 421, 443 (2013) ("With no reputable theory as to how the vaccination could cause the injury, this exercise [of evaluating the timing] is not possible").

Moreover, establishing that an injury occurred shortly after vaccination, by itself, does not mean that the petitioners are entitled to compensation. Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364 (Fed. Cir. 2012) (holding that the special master did not err in resolving case based upon the second prong of the Althen test); Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("Temporal association is not sufficient, however, to establish causation in fact."). The petitioners would need to establish the first and second Althen prongs, and because they have failed to do so, they are not entitled to compensation.

D. Alternative factors.

Finally, if the Copenhavers had prevailed on all three Althen prongs, then the Secretary would bear the burden of establishing some factor, other than the vaccinations, caused Nicholas's death. When the petitioners have not met their burden, as in this case, the Secretary does not bear a burden of presenting an alternative cause. LaLonde v. Sec'y of Health & Human Servs., 746 F.3d 1334, 1340 (Fed. Cir. 2014).

Thus, the Secretary's apparent abandonment of two potential alternative factors (co-sleeping and pneumonia) (see footnotes eight and nine above) does not affect the outcome of this case. The problem with the Copenhavers' case is that the evidence, taken as a whole, does not support the theory that vaccinations can serve as an extrinsic risk factor by stimulating the production of cytokines that impair the brain's functioning. The relative strength or weakness of any argument that something else caused Nicholas to die is irrelevant to assessing whether the vaccinations can contribute to a case of SIDS. See Caves, 100 Fed. Cl. at 140 n.14 ("the court agrees that the exclusion of alternative etiologies is not relevant to the issue of whether the influenza vaccine is capable of causing [transverse myelitis]").

Conclusion

As demonstrated in the moving testimony from Ms. Copenhaver, Nicholas's death has caused his parents a terrible grief. Their suffering is understandable, and they deserve much sympathy for losing a child so mysteriously.

However, sympathy cannot be a basis for deciding cases in the Vaccine Program. To be entitled to compensation, the Copenhavers are required to establish that the vaccinations contributed to Nicholas's death. They have failed to meet this burden. Therefore, the Clerk's Office is instructed to enter judgment in accord with this decision.

IT IS SO ORDERED.

S/Christian J. Moran
Christian J. Moran
Special Master